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Zoological Research

Developmental Effects of Intraperitoneal Injection of Polychlorinated Biphenyls in Rats During Pregnancy

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Abstract: Polychlorinated biphenyls (PCBs) are widespread environmental contaminants that are possible health hazards for human beings through a variety of pathways. In the present study, 50 time mated pregnant rats were divided into five groups and injected daily from gestational days 7 to 18 with either 2,2′,4,4′- tetrachlorobiphenyl (PCB 47) or 3,3′,4,4′- tetrachlorobiphenyl (PCB 77) or seseme oil (control) to evaluate the effects of these PCBs on prenatal and postnatal development. Offspring were examined for malformations of genitalia at birth and in adulthood. Body weight gains of these animals were checked every 7 days through postnatal day (PND) 119. There were no clinical signs of toxicity in the PCB-treated dams or their offspring throughout the experiment. Litter size and sex ratio of the litters were not affected. Both PCBs produced a significant increase in the females' anogenital distance, suggesting a modification of androgen responsiveness in females resulting from PCB exposure during development. Similar effects were not seen with the males. The proportion of individuals with eyes open by PND 15 was significantly reduced by both PCBs. Exposure to 1 mg/kg body weight of PCB 77 significantly reduced body weight gains in male pups from PND 35 to 119. However, no significant differences were found in body weight gains of the pups exposed to PCB 47.

Key words: PCB; Growth and development; Rat

妊娠期腹腔注射多氯联苯对大鼠生长发育的影响

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摘要: 将50只同期怀孕的大鼠分为5组, 在怀孕第7—18 d, 每天给两组大鼠腹腔分别注射1和20 mg/kg体重2,2',4,4' -四氯联苯 (PCB 47); 给另两组分别注射0.25和1 mg/kg体重3,3',4,4' -四氯联苯 (PCB 77); 对照组注射0.1 mL芝麻油。幼鼠出生时记录每窝产仔数和性比; 出生后每隔7 d称体重直到第119 d; 出生后第15天时检查幼鼠的睁眼率。与对照组相比, PCB 47和PCB 77所有剂量组每窝产仔数和性比无显著差异; PCB 47 (20 g/kg体重组) 和PCB 77 (两个剂量组) 雌幼鼠肛门—生殖孔距离显著增加, 出生后15 d幼鼠的睁眼率显著降低; PCB 77 (1 mg/kg体重组) 雄幼鼠从出生后第35至119天体重显著降低。提示PCB 77主要影响雄鼠的生长发育。

关键词: 多氯联苯; 生长发育; 大鼠
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Polychlorinated biphenyls (PCBs) are classified as a priority pollutant by the US Environmental Protection Agency that are detected in the air, water, sediments, wildlife, human adipose tissue, milk, and serum (Jensen & Sundstrom, 1974; Jacobson et al, 1984; Koopman-Esseboom et al, 1994; Moore et al, 1997). PCBs have been shown to be developmental toxins in both laboratory animals and humans, and the

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effects include congenital malformations, increases in fetal mortality and neurobehavioral alterations (Peterson et al, 1993). Both epidemiological investigations in children (Jacobson et al, 1992) and experimental studies in laboratory animals (Seegal et al, 1997; Weinand-Harer et al, 1997) have revealed the importance of prenatal exposure for later neurobehavioral impairment. Detrimental effects of PCBs have been reported in accidentally contaminated human, experimentally treated rats and environmentally exposed birds (Higuchi, 1976; Hoffman et al, 1987, 1993; Seegal et al, 1997). Reproductive toxicity of many PCB congeners and mixtures has been assessed. Brouwer & ven den Berg (1986) demonstrated that metabolites of 3, 3′, 4, 4′- tetrachlorobiphenyl (PCB 77) blocked the binding sites of vitamin A and thyroid hormones at their *plasma* transport protein complex, thereby leading to a decrease in total and free T4 levels and a decrease in plasma retinol. Aroclor 1254 delayed the righting reflex and ear opening, accelerated eye opening (Bowers et al, 2004). Seegal et al (1997) found no effects of 2, 2′, 4, 4′-PCB (PCB 47) at the doses of 1, 10 and 20 mg/kg body weight and PCB 77 at the doses of 0.25 and 1 mg/kg body weight on the number of pups per litter, sex ratio and body weight at birth, however, PCB 77 decreased the body weight development of the pups from postnatal days (PND) 3 to 90.

In the study by Seegal et al (1977), the data collected were before PND 90 when the male rat reaches sexual maturity. Obviously there is a question that needs to be answered about what effects will be after PND 90, especially after the male pup rat reaches developmental maturity. In this study, we used rat as a model to evaluate the effects of prenatal exposure to the dioxin-like PCB congener PCB 77, and the noncoplanar di-ortho-substituted PCB congener, PCB 47, on the development of body weight in the laboratory rat. Special attempts were given to investigate if the decrease in body weight gain of the pup rats is temporary or permanent. To the best of our knowledge, there have not been any studies in the literature related to ours.

1 Materials and Methods

1.1 Animals

Fifty time mated Long-evans female rats (*Rattus norvegicus*) were purchased from the Harlan-Sprague Dawley Inc. (Indianapolis, IN, USA). Upon arrival, the rats were divided into five groups and one female was housed to a cage (50 cm × 25 cm × 20 cm). These animals were maintained in an air-conditioned room at (23 ± 2) ℃ under a 12∶12 light/dark cycle with lights on from 19: 00 to 07: 00 and a relative humidity of 55%. Food (Harlan Teklad 22/5 rodent diet #8640, Madison, WI, USA) and tap water were available *ad libitum*.

1.2 Drugs and injections

Both PCB 47 and PCB 77 were purchased from AccuStandard (New Haven, CT, USA) and dissolved in sesame oil (Sigma, St.Louis, MO, USA). The dams were injected daily with either PCB 47 at the dosage of 1 or 20 mg/kg body weight or PCB 77 at the dosage of 0.25 or 1 mg/kg body weight or sesame oil (control group) from gestational days 7 to 18. These treatment levels were adapted from studies showing developmental effects of these congeners on brain dopamine (Seegal et al, 1977). While the dose levels used in this experiment parallel those used by Seegal et al, the routes of administration differed. We administered the PCBs through intraperitoneal injections, as was done in other behavioral studies using PCB mixture (Chung & Clemens, 1999; Chung et al 2001). The dams were weighed every 3 days during gestation and the amount of PCB was adjusted in accordance with changes in body weight.

1.3 Developmental measurement

At birth, the number of pups per litter, the sex ratio of the litter, and the anogenital distance and body weight of the individual pups were determined. Litters were culled to four male and four female pups within the first 24 h after birth. When necessary, additional offspring from identically treated dams were used to maintain the desired sex ratio and the number of pups per litter. The dams that donated pups provided them to a single litter. The body weights of the offspring were recorded weekly for the duration of the experiment. As an additional measure of general development, each pup was checked for eye opening on PND 15. At weaning, the animals were segregated by sex and treatment, and housed in plastic cages (50 cm × 25 cm × 20 cm). The genitalia of these animals were examined for malformations at birth and in adulthood.

1.4 Data analyses

The data for the sex ratio/litter at birth and the eyes opening on PND 15 were analyzed by the chi-square method and anogenital distance data were con-

ducted using Kruskal-Wallis one-way ANOVA on ranks and pair-wise comparisons were done by Dunnett's method. Data for body weight growth were assessed by two-way ANOVA (dose × age) and when significant interactions were noted one-way ANOVA combined with Student-Newman-Keuls tests were applied.

2 Results

2.1 Effect on sex ratio and litter size

There were no clinical signs of toxicity in the PCB-treated dams and their offspring throughout the experimental period. No significant differences were found in the number of pups per litter between the PCB-exposed groups and the control (Table 1). There were no statistically significant differences in the sex ratio of the litters across the treatment groups (Table 1).

2.2 Effect on anogenital distance at birth

Both doses of PCB 77 significantly increased the female anogenital distance at birth compared to the control group ($H = 10.81$, $P < 0.01$), whereas PCB 47 increased the female anogenital distance ($H = 7.93$, $P < 0.05$) only in the group exposed to 20 mg/kg body weight. However, there were no significant differences in anogenital distance at birth in male pups between prenatally PCB-exposed and control groups (Table 2).

2.3 Effect on eyes opening

Both PCB 47 and PCB 77 significantly decreased the percentage of individual's eyes opened on postnatal day 15 (Table 3) in all the PCB-exposed groups (PCB 47: female: $\chi^2 = 11.34$, $P < 0.01$; male: $\chi^2 = 14.01$, $P < 0.001$; PCB 77: female: $\chi^2 = 14.69$, $P < 0.001$; male: $\chi^2 = 16.27$, $P < 0.001$). The proportion of individuals with eyes open by PND 15 was significantly reduced in the two groups receiving PCB 77 and in the group treated with the higher dose of PCB 47. The effects were evident in both male and female offspring (Table 3).

2.4 Effect on body weight gain

Table 1 Litter size and birth sex ratio of pups prenatally exposed to PCBs

Treatment (mg/kg)	n	Litter size (Mean ± SE)	Sex ratio (Male: Female pups)
PCB 47　1	10	12.0 ± 0.9	51.7:48.3
PCB 47　20	10	11.0 ± 1.0	53.6:46.4
PCB 77　0.25	9	11.6 ± 1.0	45.2:54.8
PCB 77　1	10	11.4 ± 0.5	50.0:50.0
Control (0.1 mL oil)	10	10.7 ± 1.3	58.9:41.1

PCB 47: $\chi^2 = 1.25$, $df = 2$, $n = 30$, $P = 0.536$; PCB 77: $\chi^2 = 4.09$, $df = 2$, $n = 29$, $P > 0.05$.

Table 2 Effect of prenatal exposure to PCBs on anogenital distance at birth in rat pups

Treatment (mg/kg)	n	Anogenital distance (mm) (Mean ± SE)	
		Male	Female
PCB 47　1	10	3.82 ± 0.10	2.40 ± 0.04
PCB 47　20	10	3.92 ± 0.19	2.51 ± 0.03*
PCB 77　0.25	9	3.98 ± 0.10	2.49 ± 0.03**
PCB 77　1	10	3.89 ± 0.10	2.51 ± 0.04**
Control (0.1 mL oil)	10	3.83 ± 0.12	2.37 ± 0.02

n = number of litters. * $P < 0.05$; ** $P < 0.01$ vs. control. PCB 47: $H = 7.93$, $df = 2$, $n = 30$; PCB 77: $H = 10.81$, $df = 2$, $n = 29$.

Table 3 Effect of prenatal exposure to PCBs on eye-opening on PND 15 in rat pups

Treatment (mg/kg)	n	Individuals with eyes opened (Mean ± SE)	
		Male	Female
PCB 47　1	30	2.4 ± 0.2	2.7 ± 0.2
PCB 47　20	30	1.7 ± 0.3***	2.0 ± 0.3**
PCB 77　0.25	27	1.6 ± 0.3***	2.1 ± 0.4*
PCB 77　1	30	1.6 ± 0.4***	1.6 ± 0.4***
Control (0.1 mL oil)	30	2.9 ± 0.1	2.9 ± 0.1

n = number of pups. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ vs. control. PCB 47: female: $\chi^2 = 11.34$, $df = 2$, $n = 90$; male: $\chi^2 = 14.01$, $df = 2$, $n = 90$. PCB 77: female: $\chi^2 = 14.69$, $df = 2$, $n = 87$; male: $\chi^2 = 16.27$, $df = 2$, $n = 87$.

Table 4 Postnatal body weight gains (g) of offspring prenatally exposed to PCBs

PND	PCB 47				PCB 77				Control($n=10$)	
	1 mg/kg($n=10$)		20 mg/kg($n=10$)		0.5 mg/kg($n=10$)		1 mg/kg($n=10$)			
	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male
0	5.5 ± 0.4	6.1 ± 0.1	6.1 ± 0.1	6.3 ± 0.1	6.0 ± 0.1	6.1 ± 0.1	5.8 ± 0.1	6.1 ± 0.1	6.1 ± 0.1	6.2 ± 0.1
7	16.1 ± 0.3	16.5 ± 0.4	16.3 ± 0.5	16.9 ± 0.7	16.0 ± 0.6	16.2 ± 0.7	15.7 ± 0.6	16.0 ± 0.6	15.9 ± 0.3	16.3 ± 0.4
14	34.4 ± 1.3	35.1 ± 1.1	34.7 ± 0.8	35.6 ± 0.7	33.1 ± 0.8	34.2 ± 0.5	34.0 ± 1.2	34.8 ± 1.0	34.0 ± 1.1	34.1 ± 1.2
21	54.4 ± 1.2	55.6 ± 0.9	53.1 ± 2.3	54.6 ± 2.4	53.3 ± 1.2	54.9 ± 1.3	53.4 ± 1.3	54.9 ± 0.9	52.6 ± 1.4	53.9 ± 1.4
28	86.7 ± 1.4	89.6 ± 1.1	86.7 ± 1.9	89.9 ± 2.6	85.7 ± 1.8	88.0 ± 3.0	82.2 ± 1.7	84.0 ± 1.7	85.1 ± 2.0	90.6 ± 1.6
35	129.0 ± 1.7	144.4 ± 3.0	125.3 ± 2.5	147.3 ± 3.7	123.2 ± 2.5	141.9 ± 5.1	118.4 ± 2.1	131.0 ± 3.5*	124.1 ± 2.7	151.8 ± 2.7
42	159.9 ± 1.9	196.4 ± 3.9	151.7 ± 3.2	199.8 ± 5.4	153.7 ± 3.1	189.9 ± 6.8	149.0 ± 2.3	178.3 ± 6.3*	153.8 ± 2.7	207.4 ± 4.0
49	184.8 ± 3.4	249.1 ± 5.5	171.9 ± 4.7	251.3 ± 7.0	175.6 ± 4.1	238.8 ± 9.6	171.4 ± 3.5	224.3 ± 9.2*	174.8 ± 4.1	257.6 ± 3.8
56	206.4 ± 3.4	296.1 ± 6.3	191.7 ± 6.4	303.5 ± 9.1	196.4 ± 4.4	289.3 ± 10.5	192.3 ± 3.5	268.3 ± 11.9*	196.9 ± 4.8	304.8 ± 5.7
63	222.2 ± 4.9	336.3 ± 7.6	203.9 ± 7.0	332.5 ± 10.0	210.9 ± 5.6	326.2 ± 12.0	212.7 ± 3.9	302.1 ± 13.9*	207.1 ± 6.5	349.9 ± 6.9
70	234.2 ± 5.6	373.8 ± 8.7	227.1 ± 7.1	364.9 ± 11.4	230.2 ± 5.5	360.0 ± 11.5	225.8 ± 5.2	333.8 ± 17.3*	229.0 ± 5.9	384.0 ± 7.7
77	244.9 ± 4.3	408.9 ± 9.4	238.4 ± 5.7	397.3 ± 12.9	243.2 ± 5.4	388.4 ± 12.8	237.6 ± 5.2	363.4 ± 17.2*	241.7 ± 5.9	417.3 ± 8.1
84	253.9 ± 4.3	435.8 ± 10.4	247.7 ± 5.8	418.6 ± 13.2	249.4 ± 4.9	418.7 ± 13.3	242.5 ± 4.4	382.1 ± 20.0*	245.8 ± 5.6	442.7 ± 8.5
91	259.4 ± 5.1	458.5 ± 11.1	252.7 ± 6.1	438.4 ± 13.5	258.0 ± 4.3	431.7 ± 14.1	253.2 ± 5.3	397.7 ± 20.9*	262.8 ± 6.5	461.9 ± 8.7
98	272.0 ± 6.1	477.2 ± 12.1	263.6 ± 6.2	461.0 ± 14.4	272.9 ± 4.7	456.7 ± 15.1	259.9 ± 5.1	417.1 ± 21.4*	270.0 ± 6.6	481.2 ± 9.2
105	280.3 ± 2.0	495.0 ± 4.5	277.0 ± 8.0	481.4 ± 15.5	286.9 ± 5.0	475.4 ± 15.1	266.4 ± 5.8	430.8 ± 22.7*	279.9 ± 8.3	504.7 ± 9.9
112	289.5 ± 9.2	519.1 ± 14.3	284.7 ± 9.3	495.9 ± 15.4	294.6 ± 6.0	490.1 ± 15.7	277.6 ± 7.4	445.8 ± 24.4*	293.4 ± 10.0	519.6 ± 10.7
119	298.5 ± 10.5	532.5 ± 15.0	289.9 ± 10.2	510.0 ± 16.4	304.4 ± 6.9	504.8 ± 17.6	287.1 ± 7.5	451.1 ± 25.8*	304.9 ± 12.3	538.5 ± 11.0

* $P < 0.05$ as compared with the control group.

Treatment with PCBs did not affect the weight gain of dams during gestation. The body weight gain of the male pups exposed to PCB 77 was significantly decreased ($F_{2,36} = 1.735$, $P = 0.006$). One-way ANOVA combined with SNK tests demonstrated that the body weight gain of the male pups exposed to 1 mg/kg body weight of PCB 77 was significantly decreased from PND 35 to 119 (Table 4) compared with the control group. However, none of the other PCB treatments significantly affected the body weight gain of the male offspring. Exposure to PCBs did not affect the weight gain of the female offspring in all the PCB-treated groups.

3 Discussion

Our results demonstrate that PCB 77 (1 mg/kg body weight) decreased the body weight gain of male pups. This is consistent with the study reported by Seegal et al (1997). However, there were no significant effects on body weight gain until PND 35 in our study. This may be caused by the different paradigms of PCB exposure since the animals were removed from PCB exposure at weaning in Seegal et al's study. Moreover, the decrease in body weight gain existed until the end of our experiment (PND 119) and there was no body weight gain make-up after the pups reached sexually and developmentally mature. This suggests that the decreasing effects of PCB 77 on body weight gain in male pups are permanent. This is a key finding of our study, suggesting prenatal exposure to PCB 77 would have a detrimental impact on the body development of the animals. However, PCB 47 and PCB 77 at the dose of 0.25 mg/kg body weight did not have significant effects on the body weight gain in pups.

Both PCBs significantly increased the anogenital distance in the female offspring. Since there were no significant differences in body weight at birth we consider this increase of anogenital distance is caused by the PCB treatment. Since PCB 77 has been reported to be estrogenic as well as antiestrogenic, we were surprised to find an increase in anogenital distance, which is normally an indication of androgenic action. However, recent studies (vom Saal et al, 1997; Gupta, 2000) have shown that exposure to low doses of estrogen or estrogenic compounds often results in an increase in androgen receptors in the prostate. If parallel changes also occur in the surrounding tissues that comprise the anogenital region, this would provide a possible explanation for why we found an increase in the anogenital distance following treatment with a substance known to have estrogenic activity. While PCB 47 has not been reported to have steroidal hormone actions, its parallel effect on anogenital distance may suggest a degree of estrogenic action at the higher dose. Thus, the associated increase in anogenital distance may both reflect an estrogenic effect during perinatal development. This is consistent with earlier studies showing that reductions in the display of lordosis induced by exposure to androgens depend upon their conversion to estrogenic metabolites by the developing brain (McCarthy et al, 1993).

Although PCB exposure delayed eye opening when the animals were examined on PND 15, the treatments did not produce symptoms of general toxicity or gross malformations of the genitalia in either male or female offspring. Litter size, sex ratios of the litters, and survival of the pups were also unaffected by the PCBs. This is in contrast to the decrease in the number of live births and high neonatal mortality seen when higher doses of PCB 77 are administered during gestation (Tilson et al, 1990). However, 15 mg/kg body weight of Aroclor 1254 accelerated eye opening from gestation days 10 – 14 (Brouwer & ven den Berg, 1986). This inconsistency with our findings may be caused by the low concentration of PCB 77 in Aroclor 1254.

In summary, it appears that fetal or lactational exposure to PCB 77 results in a decrease in body weight gains in the male rat pups even beyond sexual mature. This effect was associated with an increase in fetal androgenic exposure, as indicated by an increase in the anogenital distance of the female offspring. In contrast, male offspring of PCB treated dams did not show an increase in anogenital distance at birth.

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